Request for Withdrawal of Finality of Rejection

Applicants believe that the Examiner has made the rejections final prematurely in the present application. According to MPEP § 706.07(a), second or subsequent office actions shall be final, *except*:

> where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p).

No information disclosure statements (IDS's) have been filed since the last Office Action was mailed, and thus the new rejection is clearly not based on information filed in an IDS during the period set forth in 1.97(c).

In the previous Amendment, the sole independent claim, Claim 1, was amended to recite that the solid support is "substantially planar or comprises substantially planar regions." The Examiner has introduced a new rejection under 35 U.S.C § 102(b) over Sambrook, *et al.*, allegedly necessitated by this amendment. Sambrook, *et al.* teach a method of "binding" DNA to a nitrocellulose filter, which according to the Examiner involves attaching a plurality of nucleic acids to said support to form an array and drying the array by exposing to a dry atmosphere for a period of at least 30 seconds.

While Applicants do not concede the propriety of such a rejection, according to the Examiner's statement regarding the teachings of Sambrook, *et al.*, this reference could have been applied in a rejection of Claim 1 prior to amendment. By applying Sambrook, *et al.* for the first time in a final office action, the Examiner has improperly deprived the Applicants of the opportunity to fully respond to the rejection as a matter of right. MPEP § 706.07 states that:

> The applicant who is seeking to define his or her invention in claims that will give him or her the patent protection to which he or she is justly entitled should receive the cooperation of the examiner to that end, and not be prematurely cut off in the prosecution of his or her application.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the finality of the Office Action.

Rejection of Claim 1 Under 35 U.S.C. § 102(b)

Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Sambrook, *et al.* (Reference U). The Examiner states that Sambrook, *et al.* 'teach a method of preparing a nucleic acid on a substantially planar solid support, namely a nitrocellulose filter.

Claim 1, as amended, is not anticipated by Sambrook, *et al.* Nitrocellulose membranes used in DNA isolation and hybridization studies are porous. This point is illustrated by the nitrocellulose membranes available in the Sigma-Aldrich on-line catalog; relevant pages of the catalog are enclosed herewith as "Exhibit AR". All of the nitrocellulose membranes available from Sigma-Aldrich have pores ranging from 0.22 to 8 microns in size. Thus, Sambrook, *et al.* do not disclose non-porous substrates, and consequently do not anticipate Claim 1.

Because Sambrook, *et al.* do not disclose non-porous solid substrates, Claim 1 is not anticipated by Sambrook, *et al.* Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-17 Under 35 U.S.C. § 103(a)

Claims 1-17 are rejected under 35 U.S.C. § 103(a) as being *prima facie* obvious over Torrence, *et al.* (U.S. Patent No. 5,677,289; Reference B), in view of Synthesis Cycle 10hpaf3 (hereinafter the "synthesis cycle"; Reference V), further in view of Yeung, *et al.* (Reference U), and further in view of McGall, *et al.* (U.S. Patent No. 6,147,205; Reference A). The Examiner states that it would have been obvious for one of ordinary skill in the art to dry a solid support using the synthesis cycle 10hpaf3 in the method of Torrence, *et al.* for oligonucleotide synthesis in order to remove unwanted components and to improve the quality of synthesis of the oligonucleotides. The Examiner further states that an ordinary practitioner would recognize that the selection of specific flushing times for argon represents a balance between speed of the cycle versus quality of the resultant product. The Examiner characterizes Yeung, *et al.* as providing evidence that optimization of steps such as drying is routine in the art.

As stated in MPEP § 2143, to establish a *prima facie* case of obviousness, three basic criteria are required: 1) there must be some suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference (or references when combined) must teach or suggest all the claim

limitations. Furthermore, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. The instant claims are not *prima facie* obvious in view of the cited references, because, *inter alia*, one of ordinary skill in the art would not have been motivated to combine the references as detailed below.

One of ordinary skill in the art lacked motivation to combine the teachings regarding drying a substrate disclosed in Torrence, *et al.*, the synthesis cycle, and Yeung, *et al.* with the teachings regarding the planar substrate disclosed in McGall, *et al.*, because of the significant differences in the methods used to prepare nucleic acid arrays caused by the physical differences in the supports. There are important practical and economic considerations which weight against the motivation to combine the cited references. Torrence, *et al.* and Yeung, *et al.* use controlled pore glass beads as the solid substrate (the synthesis cycle is silent as to the substrate), which are presumably in a column during nucleic acid preparation. Given the large surface area to volume ratio of such porous glass beads and the effects of surface tension and/or capillary action in the pores, one would expect that a considerable amount of liquid would remain in contact with the glass beads. Thus, a drying step is necessary to remove unwanted components and to ensure adequate product yield.

In contrast, a non-porous, planar substrate has a much smaller surface area to volume ratio and does not retain significant quantities of liquids. This feature is noted by McGall, *et al.* at column 14, lines 66-67, where the patent states that non-porous supports have improved washing efficiencies. "Biochip Technology", enclosed herewith as "Exhibit AS", provides further support for the differences in using porous and non-porous substrates. The first paragraph of page 2 of Exhibit AS states that "a non-porous substrate also prevents the absorption of reagents and sample into the substrate matrix, allowing the rapid removal of organic and fluorescent compounds during biochip fabrication and use." Based on this evidence, one would not expect a drying step to be necessary for the purpose stated by the Examiner (i.e., that a drying step "would improve removal of unwanted components and improve quality of synthesis of the oligonucleotides"). In fact, one would generally consider a drying step for non-porous, planar substrates to be undesirable. Such a drying step would lengthen the process of preparing the nucleic acids and add considerable cost and complexity to the nucleic acid preparation with little or no expected benefit. As the number of different nucleic acids in an array increases (as recited in Claims 11-17), the number of steps required to synthesize the array increases proportionally.

Given the ease of washing a non-porous, planar substrate, a drying step to remove unwanted components would have been considered superfluous. In view of the large number of synthetic steps in array preparation, repeated iterations of an unnecessary drying step are particularly undesirable, and one of ordinary skill in the art would not be motivated to add unnecessarily to the length and cost of array preparation.

Further evidence for a lack of motivation to combine the cited references is found in the lack of any teaching or suggestion therein that a non-porous, planar solid substrate can become pitted in the preparation of a nucleic acid array, let alone any teaching or suggestion of a solution to the problem of pitting. The present invention recognizes and solves the problem of pitting that occurs on non-porous, planar, solid supports during preparation of a nucleic acid array. The synthesis cycle is silent as to the type of substrate used. Torrence, *et al.* and Yeung, *et al.* both use controlled pore glass, in which it would be difficult to determine whether pitting had occurred due to the pores. McGall, *et al.* disclose non-porous substrates; however, McGall, *et al.* do not teach the pitting of such substrates. Since none of the cited references recognize the problem of pitting, no reference or combination thereof can be said to solve the problem. In contrast, the examples disclosed in the specification (pages 21-24) clearly show increased drying time reduces pitting of a substrate. This is not a showing of unexpected results stemming from the claimed method *per se* submitted to rebut a *prima facie* showing of obviousness, but rather evidence that the subject application alone provides the motivation lacking in the prior art.

In summary, it is clear that one of ordinary skill in the art would not have been motivated to combine the cited references to apply the drying step of Torrence, *et al.*, Yeung, *et al.* and the synthesis cycle to the substrates of McGall, *et al.* Thus, the Examiner has not established a *prima facie* case of obviousness. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Twice Amended) A method of reducing pitting on a solid support in the preparation of [preparing] a nucleic acid array on said [a] solid support, wherein said solid support is non-porous and substantially planar or comprises substantially planar regions, said method comprising:

a) attaching a plurality of nucleic acids to said support to form an array; and

b) drying said array by exposing to a dry atmosphere for a period of at least 30 seconds.